REMARKS

Amendments to the Specification

The Specification has been amended to correct a typographical error. No new matter has been added.

Claim Amendments

Claims 26, 37, 39 and 41 have been cancelled.

Claims 1, 6, 8, 14, 19, 28, 33, 42, 44 and 46-49 have been amended.

Rejection of Claims 1-49 Under 35 U.S.C. §112, Second Paragraph

Claims 1-49 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner states that Claims 1-27 and 42-49 are indefinite over the recitation of the terms "identifying" and "identify" in Claims 1, 14, 42, 44, and 46-48. The Examiner further states that it is unclear whether this language refers to a type of active method step or whether this language encompasses purely mental steps. The Examiner also states that Claims 1-45 and 48-49 are indefinite over the recitation of the terms "analyzing" and "analyzed" in Claims 1, 14, 28, 42, 44, and 48, in that it is unclear whether this language refers to a type of active method step or whether this language encompasses purely mental steps. The Examiner further states that the claims are indefinite over the recitation of the terms "selected" and "selecting" in Claims 1, 12,14, 24, 28, 31, and 46-48. The Examiner states that it is unclear whether this language refers to a type of active method step or whether this language encompasses purely mental steps.

Applicants note that the Specification, page 15, lines 4-10, makes clear that the steps of the claimed methods can be carried out physically or virtually (i.e., without physical or actual manipulation, such as in a computer system).

The Examiner states Claims 1-27 and 44-49 are indefinite over the recitation of the phrases "corresponding to the same chromosomal location" in Claims 1, 14, and 48 and "corresponding chromosomal locus" in Claims 46-47. The Examiner further states that it is unclear what type of relationship between a nucleic acid and a chromosomal location or locus are intended to be encompassed by the term "corresponding". The Examiner also states it is unclear

what actual steps must be carried out in order to practice the claimed methods and that the metes and bounds of the claims are unclear.

Applicants note that Claims 1, 14 and 46-48 have been amended to recite that the pairs of fragments are from the same chromosomal location. Support for this amendment can be found throughout the Specification, for example, at page 12, line 27, through page 13, line 6.

The Examiner states that Claims 1-13 are indefinite for failing to recite a final process step that clearly relates back to the claim preamble. The Examiner states that the claims do not set forth how comparing pairs of orthologous sequences results in identifying a collection of polymorphisms. The Examiner concludes that it is unclear as to whether the claims are intended to be drawn to methods for identifying a collection of polymorphisms or methods for comparing orthologous sequences to identify polymorphisms between said sequences.

Applicants note that Claim 1 has been amended to recite a final process step that clearly relates back to the claim preamble.

The Examiner states that Claims 6-7and 19-20 are indefinite over the recitation of the phrase "particular" in Claim 6 and 19. The Examiner states that it is unclear how the term is intended to limit the term "trait".

Applicants note that Claims 6 and 19 have been amended to delete the word "particular".

The Examiner states that Claims 8-9 are indefinite over the recitation of the phrase "wherein step (b)(i) is performed by one or more restriction endonucleases". The Examiner states that this language suggests that a restriction endonuclease will carry out a method step, rather than indicating the manner in which they are to be employed.

Applicants note that Claim 8 has been amended to recite that the step is performed "using" one or more restriction endonucleases.

The Examiner states that Claim 26 is indefinite over recitation of the language "wherein the one or more restriction endonucleases cleave DNA on average about once every 2000 base pairs".

Applicants note that Claim 26 has been cancelled.

The Examiner states Claims 28-43 and 48-49 are indefinite for failing to recite final process steps that clearly relate back to the claim preambles and over the language "methods for genotyping" and "analyzing... to assess the genotype" in Claims 28 and 48.

Claim 28 has been amended to clarify that it is drawn to a method of genotyping a nucleic acid sample in order to determine the nucleotide present at one or more polymorphic sites of a

nucleic acid fragment. Claim 48 has been amended to clarify that it is drawn to a method of genotyping a nucleic acid-containing sample from an individual to determine the nucleotide present at one or more polymorphic sites.

The Examiner states that Claims 33-35 are indefinite over the recitation of the term "specific oligonucleotide linker sequences". The Examiner states that it is unclear how the term "specific" is intended to modify the oligonucleotide linker sequences.

Applicants note that Claim 33 has been amended to delete the word "specific".

The Examiner states that Claims 37, 39, and 41 are indefinite because it is unclear how the claims are intended to further limit claim 33. The Examiner further states that it is unclear as to whether the steps recited in Claims 37, 39 and 41 are to be performed in lieu of the process set forth in Claim 33 or whether the steps of Claim 37, 39 and 41 are intended to modify the limitations set forth in Claim 33.

Applicants note that Claims 37, 39 and 41 have been cancelled.

The Examiner states that Claims 42-45 are indefinite over the recitation of the phrase "sequences of the two members of a proposed pair" and "proposed pair" in Claims 42 and 44. The Examiner states that there is insufficient antecedent basis for the language. The Examiner further states that it is unclear as to what types of pairs might be considered "proposed" pairs and how such pairs relate back to pairs of fragments of Claims 1 and 14.

Applicants note that Claims 42-44 have been amended to recite "comparing the sequence of two fragments from the reduced representation".

The Examiner states that Claims 42-45 are indefinite over the recitation of the phrase "identical over 10 or more bases within the first 50 bases and the last 50 bases of the sequences". The Examiner states that it is unclear as to whether this language is intended to require identity over 10 bases combined, or over 10 bases within each of the first 50 and last 50 bases of the sequence. The Examiner also states it is unclear as to whether the language "identical over" is intended to require identity over 10 contiguous bases, or whether the claims are intended to encompass identity at any 10 positions within the first and/or last 50.

Applicants note that Claims 42 and 44 have been amended to recite "if the two sequences are identical over 10 or more contiguous bases within each of the first 50 bases and the last 50 bases of the sequences". Support for this amendment can be found throughout the Specification, for example, at page 24, line 22, through page 25, line 19.

The Examiner states that Claims 42-45 are indefinite over the recitation of the term "candidate single nucleotide polymorphisms" in Claims 42 and 44. The Examiner states that it is unclear what is meant by this language and how a candidate single nucleotide polymorphism would differ from a single nucleotide polymorphism within the context of the claimed invention.

Applicants respectfully traverse this rejection. The function of the recited method step is to identify fragments which are truly orthologous (from the same chromosomal location) and to eliminate fragments which are not truly orthologous. For example, fragments which are highly homologous but from different chromosomal locations, or duplicate loci (repeats) are to be excluded (see page 13, lines 7-12). Sequence variations between sequences which are not orthologous are not true polymorphisms. In this context, a "candidate" polymorphism is a polymorphism which has not yet been validated as a true polymorphism (an allelic variation between orthologous sequences) (see page 25, line 25, through page 26, line 13).

The Examiner states that Claims 42-45 are indefinite over the recitation of the phrase "determining the number of candidate matches for the same chromosomal location, wherein said candidate matches are accepted if said number of matches does not exceed expectations". The Examiner first states that there is insufficient antecedent basis for the term "the same chromosomal location", and also states that it is unclear what the scope of this term might be. The Examiner further states that it is unclear whether the language "matches are accepted" requires an actual active method step and if so how the acceptance would be accomplished. The Examiner also states that the phrase "if said number of matches does not exceed expectations" is vague because it is unclear what might constitute expectations and how a number that "does not exceed expectations" would be established or determined.

Applicants respectfully traverse this rejection. First, step (c) of Claims 1 and 14 recites "the same chromosomal location", thereby providing antecedent basis for this phrase in Claims 42 and 44. Furthermore, Applicants believe that the phrase "does not exceed expectations" is sufficiently clear when read in light of the Specification, particularly page 26, line 14, through page 27, line 14.

The Examiner states that Claims 43 and 45 are indefinite over the recitation of the phrase "wherein said expectations are determined according to binomial or Poisson distributions". The Examiner states that this language does not appraise one of skill in the art as to what actual active steps are to be taken in order to determine expectations. The Examiner further states that it is unclear how one is to employ "binomial or Poisson distributions" to determine expectations.

Applicants respectfully believe that Claims 43 and 45 are sufficiently definite when these claims are read in light of the teachings of the Specification. For example, the Specification provides guidance as how to determine the probability of identifying a SNP with minor allele frequency *p* Poisson sampling (see page 19, line 22, through page 20, line 10). Moreover, Poisson distributions and binomial distributions are standard probability tools which are well within the knowledge of the skilled artisan, and the metes and bounds of these terms are clear to one of skill in the art.

The Examiner states that Claims 46-47 are indefinite over the recitation of the language "determining a limited population of polymorphism". The Examiner states that it is unclear whether this language is intended to require one to merely detect the presence of a limited population of polymorphisms or whether the intent is to require one to determine what particular polymorphisms are present in the population. The Examiner further states that it is unclear how a "limited population of polymorphisms" would differ from a "population of polymorphisms".

Applicants note that Claims 46 and 47 have been amended to delete the word "limited".

The Examiner states that Claim 49 is indefinite because it is unclear how it is intended to further limit Claim 48. The Examiner states that it is unclear whether the recited step is to be performed in addition to the steps in Claim 48 or whether it is intended to further limit step (f) of Claim 48.

Applicants note that Claim 49 has been amended to further clarify that the second nucleic acid-containing sample is a sample which has been treated by a method comprising fractionating the nucleic acid molecules in the sample to produce nucleic acid fragments, and selecting a subset of said nucleic acid fragments, wherein either or both of the fractionating and selecting steps are done in a sequence-dependent manner.

Applicants believe that the Claims, as amended, even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-4, 8-10, 12-17, 21-22, 24-29, 31-32 and 46-49 Under 35 U.S.C. §102(b)

Claims 1-4, 8-10, 12-17, 21-22, 24-29, 31-32, and 46-49 are rejected under 35 U.S.C. §102(b) as being clearly anticipated by Gu *et al.* (*BioTechniques 24*(5):836-837 (1998); Reference U). In making this rejection, the Examiner concludes that Applicants are entitled to a priority date of September 28, 1999 with respect to the invention of the instant claims. Applicants

do not concede that the Examiner's conclusion with regard to the priority date for the instant claims is correct, and Applicants specifically reserve the right to dispute this finding and the availability of Gu *et al.* as §102(b) prior art if necessary at a later time. However, in view of the teachings of Gu *et al.*, Applicants believe that a discussion of this matter is not necessary at this time, as Gu *et al.* clearly does not anticipate the claimed invention for the reasons discussed below. Applicants also note that Claim 26 has been cancelled herein.

The Examiner states that Gu *et al.* teach a method of identifying single nucleotide polymorphisms (SNPs) via a method comprising amplification of nucleic acids, digestion of amplification products with multiple restriction endonucleases, and separation of fragments by size on a gel, allowing the visualization of heteroduplexes which are indicative of polymorphisms. Thus, the Examiner concludes that Gu *et al.* anticipates each element of the instant claims.

Applicants respectfully disagree with the Examiner's conclusion. Applicants note that Claims 1, 14, 28 and 46-48 have been amended to recite the transitional phrase "consisting essentially of" rather than "comprising". Gu *et al.* teaches (page 836, column 2) that in their method the target sequence must be amplified with specific primers, requiring knowledge of the base composition of the target sequence to design specific PCR primers. The claimed invention, as stated in the Specification at page 3, lines 21-23, does not require PCR or knowledge of the nucleic acid sequence. For example, as described in the Specification at page 22, lines 18-26, the "nucleic acid-containing sample" can be the entire human genome, such as the genome derived from multiple individuals. Applicants note that the instant claims, as amended, do not recite that the nucleic acid-containing sample is subsequently amplified utilizing PCR, and in fact this is not a necessary element of the claimed method. Thus, Applicants respectfully submit that the Claims, as amended, are not anticipated by the teachings of Gu *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 6-7, 19-20, 36, 38 and 40 Under 35 U.S.C. §103(a)

Claims 6-7, 19-20, 36, 38, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu *et al.* in view of Landegren *et al.* (*Genome Res.* 8(8):769-776 (1998); Reference V). Applicants once again reserve the right to dispute the Examiner's finding with regard to the priority date of the rejected claims and the availability of Gu *et al.* and/or Landegren *et al.* as §102(b) prior art if necessary at a later time. However, in view of the teachings of Gu *et al.* and Landegren *et al.*, Applicants believe that a discussion of this matter is not necessary at this

time, as the cited references clearly do not render the claimed invention obvious for the reasons discussed below.

The Examiner states that Gu *et al.* does not teach or suggest identification of polymorphisms found in individuals that share traits, as required by Claims 6-7 and 19-20, and that Gu *et al.* does not teach or suggest employing in their methods steps of single-base extension, hybridization to an array, and/or oligo ligation, as recited in Claims 36, 38, and 40. The Examiner states that Landegren *et al.* teach that SNPs are expected to take the place of simple tandem repeat polymorphisms -microsatellites- as markers in disease gene mapping, that SNPs are more stably inherited than microsatellites, and that identification of SNPs may facilitate detection and understanding of mechanisms underlying disease. The Examiner states that in view of the teaching of Landegren *et al.* it would have been prima facie obvious to have modified Gu *et al.* to identify polymorphisms in individuals sharing a trait, and that an ordinary artisan would have been motivated to modify Gu *et al.* in this manner for the advantage of rapidly identifying novel, candidate disease-linked or disease-causing polymorphisms. The Examiner further states that in view of Landegren *et al.* it would have been prima facie obvious to modify the analyzing step of Gu *et al.* to assess the genotype using steps of single-base extension, hybridization to an array, and oligo ligation since Landegren *et al.* teach that each of these procedures are well known methods for rapid detection and differentiation of SNPs.

Applicants respectfully disagree. As discussed above, Gu *et al.* teaches that in their method the target sequence must be amplified with specific primers, requiring knowledge of the base composition of the target sequence to design specific PCR primers. The claimed invention does not require PCR or knowledge of the nucleic acid sequence. The instant claims, as amended, do not recite that the nucleic acid-containing sample is subsequently amplified utilizing PCR, and in fact this is not a necessary element of the claimed method. Accordingly, Gu *et al.* do not anticipate or render obvious Claims 1-4, 8-10, 12-17, 21-22, 24-29, 31-32, and 46-49. Since Claims 6-7, 19-20, 36, 38, and 40 incorporate all of the limitations of the claims from which they depend, Gu *et al.* also does not anticipate or render obvious 6-7, 19-20, 36, 38, and 40.

Landegren *et al.* does not remedy the defects of Gu *et al.* Landegren et al. state on page 769 (2nd column, bottom) that SNP analyses extend from investigation of small numbers of sequence variants known to be associated with a specific disease to investigations of markers across the genome. Therefore, Landegren *et al.* suggests the use of known markers or known variants associated with disease and does not suggest identifying novel polymorphisms.

Additionally, Landegren *et al.* state on page 770 (first column) that all current methods involve target sequence amplification, and also state on page 773 (2nd column, bottom) that DNA amplification, used in all methods reported therein, elegantly solves the problem of specificity by requiring two target recognition events, one by each primer, to detect a particular sequence. Thus, Landegren *et al.* teach that all SNP-related methods require PCR amplification of known target sequences. While Applicants do not concede that one of skill in the art would have been motivated to combine the teachings of Gu *et al.* and Landegren *et al.*, even such combination would not provide a reasonable expectation of success in producing the claimed invention, as the teachings of Landegren *et al.* further support the disclosure of Gu *et al.* that PCR amplification is a necessary component of SNP discovery methods prior to the subject invention. Thus, Gu *et al.* and Landegren *et al.*, either alone or in combination, do not render the claimed invention obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 5 and 18 Under 35 U.S.C. §103(a)

Claims 5 and 8 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gu *et al.* in view of Wu *et al.* (*DNA* 8(2):135-142 (1989); Reference W). Applicants once again reserve the right to dispute the Examiner's finding with regard to the priority date of the rejected claims and the availability of Gu *et al.* as §102(b) prior art if necessary at a later time. However, in view of the teachings of Gu *et al.* and Wu *et al.*, Applicants believe that a discussion of this matter is not necessary at this time, as the cited references clearly do not render the claimed invention obvious for the reasons discussed below.

The Examiner states that Gu *et al.* do not teach or suggest analyzing RNA molecules to identify a collection of polymorphisms. The Examiner also states that Wu *et al.* teach that the identification of SNPs in RNA samples allows one to analyze the presence of mutations in RNA by determining the ratio of normal to mutant gene transcripts in an individual, and that methods of SNP analysis may be applied equally to DNA and RNA, making it possible to analyze the expression of polymorphic sequences. The Examiner further states that it would have been *prima facie* obvious to have modified Gu *et al.* to analyze an RNA sample. The Examiner concludes that an artisan would have been motivated to have made such a modification for the advantage of detecting and analyzing the presence of polymorphisms in expressed genes, as suggested by Wu *et al.*

Applicants respectfully disagree. As discussed above, Gu *et al.* teaches that in their method the target sequence must be amplified with specific primers, requiring knowledge of the base composition of the target sequence to design specific PCR primers. The claimed invention does not require PCR or knowledge of the nucleic acid sequence. The instant claims, as amended, do not recite that the nucleic acid-containing sample is subsequently amplified utilizing PCR, and in fact this is not a necessary element of the claimed method. Accordingly, Gu *et al.* do not anticipate or render obvious Claims 1-4, 8-10, 12-17, 21-22, 24-29, 31-32, and 46-49. Since Claims 5 and 8 incorporate all of the limitations of the claims from which they depend, Gu *et al.* also does not anticipate or render obvious Claims 5 and 8.

Wu *et al.* teach that *in situ* dot hybridization of DNA or RNA with an allele-specific oligonucleotide probe works equally well. Wu *et al.* do not teach any method for identifying new polymorphisms by analysis of RNA, but rather teach the use of a known polymorphism-specific probe on a spot of total RNA isolated from an individual (page 137, first column; page 139, 2nd column) to determine its presence or absence. While Applicants do not concede that one of skill in the art would have been motivated to combine the teachings of Gu *et al.* and Wu *et al.*, even such combination would not provide a reasonable expectation of success in producing the claimed invention. Even the use of RNA in the methods of Gu *et al.* does not render the claimed invention obvious, as Gu *et al.* teaches that in their method the target sequence must be amplified with specific primers, requiring knowledge of the base composition of the target sequence to design specific PCR primers. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 11, 23 and 30 Under 35 U.S.C. §103(a)

Claims 11, 23, and 30 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gu *et al.* in view of Bonn *et al.* (U.S. Patent No. 5,585,236; Reference A). Applicants once again reserve the right to dispute the Examiner's finding with regard to the priority date of the rejected claims and the availability of Gu *et al.* as §102(b) prior art if necessary at a later time. However, in view of the teachings of Gu *et al.* and Bonn *et al.*, Applicants believe that a discussion of this matter is not necessary at this time, as the cited references clearly do not render the claimed invention obvious for the reasons discussed below.

The Examiner states that Gu *et al.* do not teach or suggest a step of separating "fractionated" nucleic acids that is performed using high pressure liquid chromatography, as

required by the instant Claims. The Examiner further states that Bonn *et al.* teach an HPLC-based method which may be used to separate fractionated nucleic acids. The Examiner concludes that in view of the teachings of Bonn *et al.* it would have been *prima facie* obvious to an artisan to modify the method of Gu *et al.* so as to have separated restricted/fractionated nucleic acids by the chromatographic method of Bonn *et al.* The Examiner also states that an artisan would have been motivated to make such a modification for the advantage of improving the efficiency of nucleic acid separation and facilitating the adaptation of the method for automation, as suggested by Bonn *et al.*.

Applicants respectfully traverse this rejection. Once again, Gu *et al.* teaches that in their method the target sequence must be amplified with specific primers, requiring knowledge of the base composition of the target sequence to design specific PCR primers. Bonn *et al.* states (column 3, lines 23-27) that samples containing mixtures of nucleic acids may result from total synthesis of nucleic acids, cleavage of DNA or RNA with restriction endonucleases, as well as nucleic acid samples which have been multiplied and amplified using polymerase chain reaction techniques. While Applicants do not concede that one of skill in the art would have been motivated to combine the teachings of Gu *et al.* and Bonn *et al.*, even such combination would not provide a reasonable expectation of success in producing the claimed invention. The combination of the two references does not in any way teach or suggest a method of identifying polymorphisms which does not require amplification of the target sequences. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 33-35 Under 35 U.S.C. §103(a)

Claims 33-35 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gu *et al.* in view of Drmanac (U.S. Patent No. 6,025,136; Reference B). Applicants once again reserve the right to dispute the Examiner's finding with regard to the priority date of the rejected claims and the availability of Gu *et al.* as §102(b) prior art if necessary at a later time. However, in view of the teachings of Gu *et al.* and Drmanac *et al.*, Applicants believe that a discussion of this matter is not necessary at this time, as the cited references clearly do not render the claimed invention obvious for the reasons discussed below.

The Examiner states that while Gu *et al.* teach sequencing of orthologous sequences, Gu *et al.* do not teach or suggest particular steps that may be taken to accomplish sequencing. Examiner further states that Drmanac *et al.* discloses that the sequencing of multiple restriction

fragments by ligation of adaptors to the restriction fragments and amplification of those fragments with primers that hybridize to adaptor sequences. The Examiner concludes that in view of the teachings of Drmanac *et al.*, it would have been *prima facie* obvious to an artisan to modify the method of Gu *et al.* so as to have employed Drmanac's method for sequencing. The Examiner further states that an artisan would have been motivated to have modified the method of Gu *et al.* so as to have performed adaptor ligation and amplification with universal primers for the advantages of efficiency.

Applicants respectfully traverse this rejection. Once again, Gu *et al.* teaches that in their method the target sequence must be amplified with specific primers, requiring knowledge of the base composition of the target sequence to design specific PCR primers. While Applicants do not concede that one of skill in the art would have been motivated to combine the teachings of Gu *et al.* and Drmanac *et al.*, even such combination would not provide a reasonable expectation of success in producing the claimed invention. The combination of the two references does not in any way teach or suggest a method of identifying polymorphisms which does not require amplification of the target sequences. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 37, 39 and 41 Under 35 U.S.C. §103(a)

Claims 37, 39, and 41 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gu *et al.* in view of Drmanac *et al.*, as applied to claims 33-35 above, and further in view of Landegren *et al.* Claims 37, 39 and 41 have been cancelled herein, obviating the rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDMENTS

MARKED-UP VERSION OF AMENDMENTS TO THE SPECIFICATION

Page 18, lines 7 through 16, (amended):

The methods of the present invention can be used in humans and non-humans. For example, the methods can be used to assay polymorphisms in animals for veterinary purposes. For instance, they can be used to amplify target sequences known to be associated with susceptibilities to diseases with genetic components, or to detect known genetic defects in purebred animals such as dogs or horses. They can also be used to assess levels of biodiversity in populations of animals, plants, or microorganisms. The invention can be applied in the search for beneficial genetic components in animals and plants, both domesticated and wild, that are used for food, feed, fiber, oils, lumber, or other raw materials. They can be applied in the search for genetic components of strains of pests, parasites or disease organisms that are especially virulent to humans, plants or animals.

MARKED-UP VERSION OF CLAIM AMENDMENTS

Claims 26, 37, 39 and 41 have been cancelled.

Claims 1, 6, 8, 14, 19, 28, 33, 42, 44 and 46-49 have been amended as follows:

1. (Amended) A method for identifying a collection of polymorphisms from nucleic acid molecules in a sample by analyzing a subset of the molecules, [comprising] consisting essentially of the steps of:

a. obtaining a nucleic acid-containing sample;

b. treating the nucleic acid molecules in said sample to produce a reduced representation of nucleic acid fragments selected in a sequence-dependent manner by a method comprising:

i. fractionating said nucleic acid molecules to produce nucleic acid fragments; and

ii. selecting a subset of said nucleic acid fragments,

wherein either (i) or (ii) or both (i) and (ii) are performed in a sequence-dependent manner;

c. analyzing the reduced representation to identify pairs of fragments [corresponding to] from the same chromosomal location, wherein fragments [corresponding to] from the same chromosomal location are orthologous sequences; and

d. comparing pairs of orthologous sequences to identify polymorphisms between said sequences,

thereby identifying a collection of polymorphisms.

6. (Amended) The method of Claim 3, wherein the individuals share a [particular] trait.

8. (Amended) The method of Claim 1, wherein step (b)(i) is performed [by] using one or more restriction endonucleases.

14. (Amended) A method for identifying a collection of polymorphisms from nucleic acid molecules in a sample by analyzing a subset of the molecules, [comprising] consisting essentially of the steps of:

a. obtaining a nucleic acid-containing sample to be assessed;

b. treating nucleic acid molecules in said sample to produce a reduced representation of nucleic acid fragments selected in a sequence-dependent manner by a method comprising:

i. fractionating said nucleic acid molecules with one or more restriction endonucleases to produce nucleic acid fragments; and

ii. selecting a subset of said nucleic acid fragments using size fractionation;

wherein either (i) or (ii) or both (i) and (ii) are performed in a sequence-dependent manner;

c. analyzing the reduced representation to identify pairs of fragments [corresponding to] from the same chromosomal location, wherein fragments [corresponding to] from the same chromosomal location are orthologous sequences; and

d. comparing pairs of orthologous sequences to identify polymorphisms between said orthologous sequences,

thereby identifying a collection of polymorphisms from said nucleic acid molecules.

19. (Amended) The method of Claim 16, wherein the individuals share a [particular] trait.

28. (Amended) A method for genotyping a nucleic acid sample to determine the nucleotide present at one or more polymorphic sites of [for polymorphisms in] nucleic acid fragments contained in a reduced representation, [comprising] consisting essentially of the steps of:

a. obtaining a nucleic acid-containing sample;

b. treating the nucleic acid molecules in said sample to produce a reduced representation of nucleic acid fragments selected in a sequence-dependent manner by a method comprising:

i. fractionating said nucleic acid molecules to produce nucleic acid fragments; and

ii. selecting a subset of said nucleic acid fragments,

wherein either (i) or (ii) or both (i) and (ii) are performed in a sequence-dependent manner; and

c. analyzing the nucleic acid fragments contained in the reduced representation to assess the genotype at one or more polymorphic sites,

thereby genotyping a nucleic acid sample to determine the nucleotide present at one or more polymorphic sites of nucleic acid fragments contained in the reduced representation.

33. (Amended) The method of Claim 28, wherein step (c) is performed by attaching [specific] oligonucleotide linker sequences to the fragments in the reduced representation and then amplifying said fragments.

42. (Amended) The method of Claim 1, wherein step (c) is performed by the following steps:

a. comparing the sequences of [the] two [members of a proposed pair] fragments from the reduced representation, wherein the two sequences are further analyzed if the two sequences are at least 80% identical over at least 80% of the length of the shorter of the two sequences;

b. aligning the two sequences identified from (a), wherein the two sequences are further analyzed if the two sequences are identical over 10 or more contiguous bases within each of the first 50 bases and the last 50 bases of the sequences;

c. identifying candidate single nucleotide polymorphisms in the sequences of (b), wherein the two sequences are further analyzed if the number of candidate single nucleotide polymorphisms does not exceed 1% of the total number of bases in the shorter of the

two sequences, wherein two sequences which meet the criteria of (a) - (c) qualify as a candidate match;

d. repeating (a) - (c) for all proposed pairs; and

e. determining the number of candidate matches for the same chromosomal location, wherein said candidate matches are accepted if said number of matches does not exceed expectations,

wherein accepted candidate matches are considered a pair.

44. (Amended) The method of Claim 14, wherein step (c) is performed by the following steps:

a. comparing the sequences of [the] two [members of a proposed pair] fragments from the reduced representation, wherein the two sequences are further analyzed if the two sequences are at least 80% identical over at least 80% of the length of the shorter of the two sequences;

b. aligning the two sequences identified from (a), wherein the two sequences are further analyzed if the two sequences are identical over 10 or more contiguous bases within each of the first 50 bases [or] and the last 50 bases of the sequences;

c. identifying candidate single nucleotide polymorphisms in the sequences of (b), wherein the two sequences are further analyzed if the number of candidate single nucleotide polymorphisms does not exceed 1% of the total number of bases in the shorter of the two sequences, wherein two sequences which meet the criteria of (a) - (c) qualify as a candidate match;

d. repeating (a) - (c) for all proposed pairs; and

e. determining the number of candidate matches for the same chromosomal location, wherein said candidate matches are accepted if said number of matches does not exceed expectations,

wherein accepted candidate matches are considered a pair.

46. (Amended) A method for determining a [limited] population of polymorphisms from nucleic acid molecules in a sample, [comprising] consisting essentially of the steps of:

a. obtaining a nucleic acid-containing sample to be assessed;

b. treating nucleic acid molecules in said sample to produce nucleic acid fragments selected in a sequence-dependent manner by a method comprising:

i. fractionating said nucleic acid molecules to produce nucleic acid fragments; and

ii. selecting a subset of said nucleic acid fragments;

wherein either (i) or (ii) or both (i) and (ii) are done in a sequence-dependent manner;

c. selecting from said subset nucleic acid fragments which occur at [a corresponding] the same chromosomal locus, thereby producing a pair, and

d. identifying polymorphisms between fragments of a pair;

thereby determining a [limited] population of polymorphisms from said nucleic acid-containing sample.

47. (Amended) A method for determining a [limited] population of polymorphisms from nucleic acid molecules in a sample, [comprising] consisting essentially of the steps of:

a. obtaining a nucleic acid-containing sample to be assessed;

b. treating nucleic acid molecules in said sample to produce nucleic acid fragments selected in a sequence-dependent manner by a method comprising:

i. fractionating said nucleic acid molecules with one or more restriction endonucleases to produce nucleic acid fragments; and

ii. selecting a subset of said nucleic acid fragments using size fractionation;

wherein either (i) or (ii) or both (i) and (ii) are done in a sequence-dependent manner;

c. [selecting] isolating from said subset nucleic acid fragments which occur at [a corresponding] the same chromosomal locus, thereby producing a pair, and

d. identifying polymorphisms between fragments of a pair;

thereby determining a [limited] population of polymorphisms from said nucleic acid-containing sample.

48. (Amended) A method for genotyping a nucleic acid-containing sample from an individual to determine the nucleotide present at one or more polymorphic sites [for polymorphisms], the method [comprising] consisting essentially of:

a. obtaining a first nucleic acid-containing sample to be assessed;

b. treating nucleic acid molecules in said sample to produce a reduced representation of nucleic acid fragments selected in a sequence-dependent manner by a method comprising:

i. fractionating said nucleic acid molecules to produce nucleic acid fragments; and

ii. selecting a subset of said nucleic acid fragments;

wherein either (i) or (ii) or both (i) and (ii) are done in a sequence-dependent manner;

c. analyzing the reduced representation to identify pairs of fragments [corresponding to] from the same chromosomal location, wherein fragments [corresponding to] from the same chromosomal location are orthologous sequences;

d. comparing pairs of orthologous sequences to identify polymorphisms between the orthologous sequences;

e. obtaining a second nucleic acid-containing sample from an individual to be assessed; and

f. analyzing said second nucleic acid-containing sample to assess the genotype at one or more polymorphisms identified in (d),

thereby genotyping a nucleic acid-containing sample from an individual to determine the nucleotide present at one or more polymorphic sites.

49. (Amended) A method according to Claim 48, wherein the second nucleic acid-containing sample is a sample which has been treated by a method comprising:

i. fractionating the nucleic acid molecules in said sample to produce nucleic acid fragments; and

ii. selecting a subset of said nucleic acid fragments;

wherein either (i) or (ii) or both (i) and (ii) are done in a sequence-dependent manner [identical to step (b)].